REMARKS

This Amendment is being entered in response to the Office Action of August 25, 2003.

In this Office Action, the Examiner issued the following Actions:

1-5. The Examiner entered the amendment of July 24, 2003 *in part.*

6. The Examiner has objected to the amendment filed on July 24, 2003 under 25 U.S.C. §132 for allegedly adding new matter.

7. The Examiner has objected to the drawings for allegedly failing to comply with 37 C.F.R. §1.84(p)(5).

8. The Examiner has objected to claim 9 on matters of form.

9-19. The Examiner has rejected claims 1-9 for allegedly failing to comply with the enablement requirement of 35 U.S.C. §112.

20-25. The Examiner has rejected claims 1-9 for allegedly failing to comply with the written description requirement of 35 U.S.C. §112.

26-28. The Examiner has rejected claims 1 and 4 as allegedly indefinite.

The applicants note that no claims were rejected on prior art. With respect to the new matter rejection, applicants have canceled the amendment in compliance with the Examiner's request. With respect to the drawing rejection, applicants have provided a table that lists the locations of the reference signs. It is the applicants' intent that this table assist the Examiner's review of the application. With respect to the matters of form, applicants have amended the claim in compliance with the Examiner's request. With respect to the allegedly indefinite claims, applicants have amended their claims to delete the allegedly indefinite terms.

The only outstanding issues appear to be Undue Experimentation and Written Description. With respect to these two issues, applicants have enclosed their response. Applicants respectfully submit that, while some experimentation may be necessary, the experimentation is merely routine experimentation and not undue experimentation. With respect to the Written Description rejection, applicants respectfully submit that they are required only to show possession of the claimed invention. It appears to the applicants that the Examiner has misunderstood the invention. Appropriate clarification may be found in the remarks to follow. Reconsideration is respectfully requested.

1-5. THE EXAMINER HAS ENTERED THE AMENDMENT OF 7/24/2003 *IN PART*, ACKNOWLEDGED THE ELECTION, AND WITHDREW VARIOUS OBJECTIONS AND/OR REJECTIONS

It was unclear to the applicants which parts of the amendment had been entered, and which parts of the amendment were not entered. Applicants are operating under the assumption that all amendments were entered except for the amendment to the specification which deleted the term "haloperidol".

To better define their invention, applicants have amended claim 1 to clarify the language used. The phrase "an antagonist of a neurotransmitter receptor" has been replaced with "a neurotransmitter receptor antagonist." The term "which leads" has been replaced with the phrase "that leads." Applicants have also corrected the spelling of "microtubule-associated protein" in claim 1. It is submitted that these are minor alternations and do not introduce new matter.

6. THE EXAMINER HAS OBJECTED TO THE AMENDMENT ALLEGING THE INTRODUCTION OF NEW MATTER

The Examiner has objected to the amendment stating:

> The amendment filed 28 July 2003 (Paper No. 6) is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The deletion of "haloperidol" constituted new matter as alters the subject matter of the Specification as filed. Applicant is required to cancel the new matter in the reply to this Office Action.

The original Amendment of July 24, 2003 read as follows:

> Please replace paragraph 1, page 8 beginning with "Other candidate antagonists..." with the following paragraph:
> Other candidate antagonists which may be utilized in steps 10 et seq. include antipsychotic medicines that are chiefly designed to produce dopamine antagonism but which also exhibit muscarinic antagonism (i.e., clozapine, olanzepine, chlorpromazine, ~~haloperidol~~).

Applicants believe they are entitled to make this amendment as a matter of right, but have chosen to withdraw the amendment to facilitate the prosecution of this application. Applicants would like the following two paragraphs to be made part of the record so that the public will be made aware of the error.

Applicants respectfully submit that the deletion of haloperidol from the specification does not constitute new matter, as it is merely a change of wording to correct an error. "A change of wording to correct an error is not new matter if one skilled in the art would appreciate not only the existence of the error in the specification but what the error is." *Ex parte Brodbeck*, 199 USPQ 230 (Pat. Off. Bd. App. 1977) at 272.

The listing of compounds found at the end of page 8, paragraph 1 is clearly a listing of compounds which "exhibit muscarinic antagonism." As one of ordinary skill in the art would appreciate, haloperidol is not such a compound. The prior art is replete with documents that demonstrate that haloperidol is a poor antagonist of muscarinic receptors. Reference may be had to. Bymaster, F.P.; Felder, C.C.; Tzavara, E.; Nomikos, G.G.; Calligaro, D.O.; Mckinzie, D.L.; Muscarinic mechanisms of antipsychotic atypicality, *Progress in Neuropsychopharmacology & Biological Psychiatry*, **2003** Oct. 27(7):1125-43. Further reference may be had to Arnt, J.; Skarsfeldt, T.; *Neuropsychopharmacology* **1998**, *18*, 63-101 as well as Bymaster, F.P.; Calligaro, D.O.; Falcone, J.F.; Marsh, R.D.; Moore, N.A.; Tye, N.C.; Seeman, P.; Wong, D.T.; Radioreceptor binding profile of the atypical antipsychotic olanzapine, *Neuropsychopharmacology* **1996**, *14*, 87-96. It is clear from the prior art that one of ordinary skill in the art would appreciate the improper identification of haloperidol as a muscarinic antagonist, which it clearly is not.

7. THE EXAMINER HAS OBJECTED TO THE DRAWINGS ALLEGING THE DRAWINGS CONTAIN REFERENCE SIGNS NOT MENTIONED IN THE SPECIFICATION.

The Examiner has objected to the drawings entered with the amendment of July 24, 2003 stating:

> The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: the numbers present in Figures 1 and 2. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The object to the drawings will not be held in abeyance.

Applicants respectfully submit that the reference signs were, in fact, mentioned in the description as filed. To assist the Examiner in locating these reference signs, the following table has been constructed. This table lists the reference sign(s) and at least one corresponding location in the original specification as filed.

Table 1: Location of Reference Signs in Specification

Reference Sign(s)	Location in Specification as Filed
Figure 1	Page 3, line 11
Figure 1, element 10	Page 4, line 8
Figure 1, element 14	Page 11, line 7
Figure 1, element 16	Page 11, line 22
Figure 1, element 18	Page 12, line 1
Figure 2	Page 3, line 13
Figure 2, element 50	Page 20, line 3
Figure 2, element 51	Page 24, line 10
Figure 2, element 52	Page 19, line 10
Figure 2, element 54	Page 19, line 11
Figure 2, element 55	Page 19, line 22
Figure 2, element 56	Page 19, line 22
Figure 2, element 58	Page 19, line 23
Figure 2, element 60	Page 20, line 14
Figure 2, element 62	Page 20, line 18
Figure 2, element 64	Page 20, line 19
Figure 2, element 66	Page 20, line 19
Figure 2, element 70	Page 20, line 20
Figure 2, element 72	Page 21, line 6
Figure 2, element 74	Page 21, line 7
Figure 2, element 76	Page 21, line 10
Figure 2, element 78	Page 21, line 10
Figure 2, element 80	Page 21, line 11
Figure 2, element 82	Page 21, line 12
Figure 2, element 84	Page 21, line 12

Applicants respectfully submit that no amendment to the specification or drawings is necessary.

8. THE EXAMINER HAS OBJECTED TO CLAIM 9 AS AMENDED DUE TO INFORMALITIES

The Examiner has objected to claim 9 on formal grounds stating:

> Claim 9 is objected to because of the following informalities: two periods between "(Original")) and "The". Appropriate correction is required.

In compliance with the Examiner's request, applicants have entered an appropriate correction.

9-19. THE EXAMINER HAS REJECTED CLAIMS 1-9 AS ALLEGEDLY NOT ENABLED DUE TO UNDUE EXPERIMENTATION

The Examiner has rejected claims 1-9 as allegedly not enabled by the specification, stating:

> 9. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
>
> 10. The claims are drawn very broadly to a method of treating Alzheimer's disease via administration of an antagonist of a neurotransmitter receptor which indirectly inhibits phosphorylation of microtubule-associated protein-2 and then administering to said patient an anticholinesterase agent in humans. The language of said claims encompasses a massive genus of as of yet unspecific neurotransmitter antagonists, none of which are identified by the Specification as filed.
>
> 11. The specification teaches a prophetic process by which one can identify a neurotransmitter antagonist with the properties necessary to satisfy the limitations of claim 1. In addition, the Specification prophetically considers practicing the claimed method with the unidentified neurotransmitter receptor antagonist and an anticholinesterase agent utilizing a "sensor" to monitor the progress of the therapy.
>
> 12. The specification fails to provide any guidance for the successful use or assessment of the claimed method, and since resolution of the various complications in regards to treating Alzheimer's disease is highly unpredictable, one of skill in the art would have been unable to practice the invention without undue trial and error experimentation. In

order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations of antagonists of neurotransmitter receptors, characterize them, and then test them for suitability to practice the claimed invention. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed method treating Alzheimer's disease in a patient.

13. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a prophetically considered compound *in vivo* based solely on its predicated performance as highly problematic (see MPEP 2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* therapeutic assays, such a disclosure would not be considered enabling since the state of Alzheimer's disease is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

14. Concerning the breadth of the claims and the nature of the invention as a therapeutic, as noted above, no examples of compounds, antibodies, nucleic acids, proteins, or other "antagonists" are provided by the instant Specification as filed or the prior art that meets the limitations of claim 1 and would be useful for treating Alzheimer's disease. While putting forth the proposition of using a neurotransmitter receptor antagonist for treating Alzheimer's disease, no evidence is present in the instant Specification or the prior art as to guide the skilled artisan to identify or use the described neurotransmitter receptor

antagonist as a therapeutic. What remains is an invitation to experiment, first to determine which neurotransmitter antagonist satisfies the limitations of claim 1, and then determine its role, and finally the course of therapy that would have a salubrious outcome {see MPEP §2164.01(a)}. Thus in the absence of guidance and working examples, the skilled artisan is confronted with an undue burden of experimentation in an unpredictable and undeveloped art to practice the invention as claimed.

15. On the amount of guidance provided by the Specification, no compounds have been disclosed that have the activity required by the claims. Screening for such compounds is an act of invention, for which insufficient guidance is provided in this Specification. Thus the Specification fails to teach the skilled artisan how to make the antagonists recited in the claims.

16. The following references are cited herein to illustrate the state of the art of Alzheimer's disease.

17. Concerning the nature of the invention, as the Specification suggests using antagonists of muscarinic acetylcholine receptors, Fisher (2000) "Therapeutic Strategies in Alzheimer's Disease" M1 Muscarinic Agonists." Jpn J. Pharmacol. **84**: 101-112 and Forlenza et al. "Muscarinic agonists reduce tau phosphorylation in non-neuronal cells via GSK-3b inhibition and in neurons." J. Neural. Transm. **107**: 1201-1212 both teach that muscarinic agonists alter the metabolism of amyloid precursor proteins leading to an increase in a-secretase cleaved and a decreased production of amyloidogenic peptides. This suggests that said compounds may have a therapeutic effect. Thus the nature of the invention runs contrary this evidence as both are silent on antagonists as therapeutics as well as the role of MAP-2 in Alzheimer's disease therapy.

18. On the prior art, as the Specification suggests that M1 antagonists may be used in the screening steps of the invention, Fisher et al. (17 January 1996) "M1 Agonists for the treatment of Alzheimer's disease. Novel properties and clinical update." Ann. N.Y. Acad. Sci. **777**: 189-196 teaches that M1 agonists may be useful as therapeutics for Alzheimer's especially due to the relationship between decreased phosphorylation of tau proteins via m1AchR (pp. 194). The reference is silent, however, on the subject of indirect phosphorylation, antagonists, and the role of MAP-2 phosphorylation thus offering no support to the claimed method.

> 19. Finally the specification does not provide a nexus between the method and a therapeutic outcome in Alzheimer's patients. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying prophetic guidance to the in vivo treatment of Alzheimer's disease as exemplified in the references herein.

In paragraph 10 of the Office Action the Examiner has stated "The language of said claims encompasses a massive genus of as of yet unspecific neurotransmitter antagonists, none of which are identified by the Specification as filed." The applicants respectfully submit that neither a narrow genus, nor the specification of an antagonist is required for a disclosure to be enabling. If the Examiner believes the genus is overly broad, he is respectfully invited to make a rejection based on prior art. If the Examiner believes the claims are indefinite, he is respectfully invited to reject the claims as indefinite. In neither of these circumstances is an enablement rejection proper.

In paragraph 11 of the Office Action the Examiner has stated "In addition, the Specification prophetically considers practicing the claimed method with the unidentified neurotransmitter receptor antagonist and an anticholinesterase agent utilizing a "sensor" to monitor the progress of the therapy." The applicants respectfully submit that the fact that an example is prophetic is not proper grounds for an enablement rejection. M.P.E.P. § 2164.02 states that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.'"

Applicants respectfully disagree with the term "unidentified." Applicants respectfully submit that they have taught a process by which the chemical agents at issue may be clearly identified. Indeed, a significant portion of the disclosure has been devoted to just such a teaching. Reference may be had, for example, to page 4, paragraph 1; Figure 1; page 8, paragraph 3 to page 10; page 11, paragraph 1. In addition to the teachings specifically included in the specification as filed, a number of prior art references were incorporated by reference which contain similar teachings.

In paragraph 12 of the Office Action the Examiner has stated "The specification fails to provide any guidance for the successful use or assessment of the claimed method..." Applicants respectfully submit that the prior art discloses a multitude of methods for diagnosing the treatment of Alzheimer's disease. It is the position of the applicants that such assessments are routine to those of ordinary skill in the art. Applicants note they are not required to detail routine methods in their specification. M.P.E.P. § 2164.01 states:

> "A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied 480 U.S. 947 (1987); and *Linde-mann Maschinenfabrik GMBH v.*

> *American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)."

Although applicants are not required to include such teachings, the applicants have elected to briefly include such disclosure anyway. Reference may be had, for example, to page 20, paragraph 1 which states:

> When the patient 50 is in the proper neurological zone, there will be decreased levels of phosphorylated tau in the spinal fluid. As is known to those skilled in the art, tau is a microtubule-associated protein. Elevated levels of phosphorylated tau in a patient's brain is a diagnostic marker for Alzheimer's disease. See, e.g., an article by K. Ishiguro et al. entitled "Phosphorylated tau in human cerebrospinal fluid: a diagnostic marker for Alzheimer's disease," appearing in Neuroscience Letters, 1999 July 30, 270 (2): 91-4. Reference also may be had to United States patents 6,194,153, 6,117,978, 6,046,381, 6,020,143, 6,020,139, 5,986,054, 5,840,540, and the like; the entire disclosure of each of these United States patents is hereby incorporated by reference into this specification.

Clearly the applicants have provided guidance for the successful use and assessment of the claimed method. The applicants further note that incorporation by reference has been deemed to be an acceptable method of complying with the enablement requirement.

> "With respect to matters necessary for an enabling disclosure and which are not common or well known, an applicant may, in the interests of economy of time and space, incorporate certain types of documents by specific reference in his application to such source materials. After ruling that prior U.S. patents may be so incorporated,...this court extended the doctrine of incorporation by reference stating as a general guideline...that any reference to a disclosure which is available to the public is permissible." *In re Howarth*, 210 USPQ at 692.

It is the applicants' position that the incorporated material is well known. Nevertheless, applicants have chosen to incorporate such material for the convenience of the reader. Applicants respectfully submit that the Examiner's rejection has been obviated.

Concerning the undue experimentation arguments presented by the Examiner in paragraphs 12-19, the applicants respectfully submit that the limited amount of experimentation that may be required would merely be routine, and not undue.

The test of enablement has been well established in the law:

> "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190, USPQ 214, 219 (CCPA 1976).

> "Time and difficulty of experiments are not determinative if they are merely routine." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Applicants provide the following table (Table 2) to illustrate that undue experimentation is not needed to identify neurotransmitter receptor antagonists that will block MAP2 phosphorylation, since neurotransmitter receptors, the second messengers, protein kinases, and finally, effects on MAP2 phosphorylation are published materials and known to those of ordinary skill in the art.

Table 2: Neurotransmitters and postsynaptic receptors having potential effects on MAP2

Neurotransmitter	**Receptors**[1]	**Second messengers**[1]	**Protein kinases/phosphatases**[1]	**Phosphorylation of MAP2**[2]
Glutamate	mGlu1, mGlu5	PI-PLC	PKC, CaCMK II	increase
Acetylcholine	M1, M3, M5	PI-PLC	PKC, CaCMK II	increase
Norepinephrine	α-1 β-1	PI-PLC AC	PKC, CaCMK II PKA	increase increase
Serotonin	5-HT2 5-HT4, 5-HT7	PI-PLC AC	PKC, CaCMK II PKA	increase increase
Dopamine	D1, D5	AC	PKA	increase

[1] mGlu: metabotropic receptor; M: muscarinic receptor; PI-PLC: phosphoinositide-specific phospholipase C; AC: adenylyl cyclase; PKC: protein kinase C; CaCMK II: calcium/calmodulin-dependent kinase II (see Siegel GJ, Agranoff BW, Albers RW, Fisher SK and Uhler MD (Eds.) Basic Neurochemistry: Molecular, Cellular and Medical Aspects, Lippincott-Raven, 1999.

[2] Sanchez C, Diaz-Nido J, Avila J. Phosphorylation of microtubule-associated protein 2 (MAP2) and its relevance for the regulation of the neuronal cytoskeleton function. Prog Neurobiol. 2000 Jun;61(2):133-68.

For the purpose of illustration, and because of the issues raised by the examiner, we will focus further discussion on M1 antagonists. In severe Alzheimer's disease, there are marked decreases in M1 receptor sites in hippocampus and parahippocampal gyrus, whereas M1 and M3 receptors show nearly normal neocortical patterns (Rodriguez-Puertas R, Pascual J, Vilaro T, Pazos A. Autoradiographic distribution of M1, M2, M3, and M4 muscarinic receptor subtypes in Alzheimer's disease. Synapse. 1997 Aug;26(4):341-50; Shiozaki K, Iseki E, Hino H, Kosaka K. Distribution of m1 muscarinic acetylcholine receptors in the hippocampus of patients with Alzheimer's disease and dementia with Lewy bodies-an immunohistochemical study. J Neurol Sci. 2001 Dec 15;193(1):23-8). Thus, any preferential binding of a M1 antagonist in limbic sites will exert a more profound functional consequence due to the already compromised state of M1 receptors in limbic sites of severe AD brain. Likewise, in mild dementia or early AD, a M1 antagonist can be more effective in limbic versus neocortical areas because of differential binding constants for muscarinic receptor subtypes in different brain areas. Methods for determining binding constants to muscarinic receptors, such as M1 and M3, are extremely well known in the art. Affinity constants are determined merely by routine experimentation. Reference may be had to page 9 of the specification

as filed, and the references cited therein. Applicants respectfully submit that routine experimentation is not undue experimentation. Applicants further submit that the time and difficulty of experiments are not determinative if they are merely routine. Moreover, the physical locations of these receptors are likewise well known. Reference may be had, for example, to Bymaster, F.P.; Felder, C.C.; Tzavara, E.; Nomikos, G.G.; Calligaro, D.O.; Mckinzie, D.L.; Muscarinic mechanisms of antipsychotic atypicality, *Progress in Neuropsychopharmacology & Biological Psychiatry*, **2003** Oct. 27(7):1125-43) who indicate that M1 receptors are preferentially localized to frontal and limbic areas (see also Moreira KM, Hipolide DC, Nobrega JN, Bueno OF, Tufik S, Oliveira MG. Deficits in avoidance responding after paradoxical sleep deprivation are not associated with altered [3H]pirenzepine binding to M1 muscarinic receptors in rat brain. Brain Res. 2003 Jul 4;977(1):31-7)..One prophetic example is S-(-)-ET 126 disclosed in Ghelardini C.; Bartolini A.; Galeotti N.; Teodori E.; Gualtieri F.; S-(-)-ET 126: a potent and selective M1 antagonist in vitro and in vivo. *Life Science*. **1996**;58(12):991-1000. S-(-)-ET 126 demonstrates an M1/M3 selectivity ratio of 178, thus it has the necessary limbic preference. Similarly, a number of other piperidinyl and tripinyl esters are known to have M1 and M3 selective antagonist properties (Xu R, Sim MK, Go ML. M3/M1-Selective antimuscarinic tropinyl and piperidinyl esters. *Eur J Pharm Sci.* **1999** Apr;8(1):39-47)..

A second prophetic example, (5R,6R)3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane (PTAC), was disclosed on page 7 of the specification as filed. Applicants respectfully reiterate that "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic'" as disclosed in M.P.E.P.§ 2164.02.

With respect to paragraph 13 of the Office Action, the applicants note that the eight factors listed were "considered in the analysis of enablement." The applicants note that the M.P.E.P. § 2164.01(a) lists these items as factors to be considered in the analysis of undue experimentation, which is merely one element of enablement. The applicants respectfully assert that the Examiner has put forth undue experimentation as a single factual determination. M.P.E.P. § 2164.01(a) states "The determination that 'undue experimentation' would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighting all the above, noted factual considerations." *In re Wands* 858 F.2d at 737, 8 USPQ2d at 1404. The Examiner seems to be asserting that the specification is not enabling because the state of Alzheimer's disease is highly unpredictable. Applicants respectfully submit that this is a conclusory statement, which lacks support. Level of predictability in the art is but one factor in an undue experimentation analysis, which in turn is one factor in an enablement analysis. Reconsideration is requested.

With respect to paragraph 14 the Examiner has stated "What remains is an invitation to experiment, first to determine which neurotransmitter antagonist satisfies the limitations of claim 1, and then determine its role, and finally the course of therapy that would have a salubrious outcome." The applicants respectfully submit that it is not necessary to determine the role of the antagonist to practice the claimed invention. Likewise, the applicant is not laying claim to a method of monitoring the course of therapy. If any experimentation is necessary, it is only routine experimentation to determine which antagonist meets the criteria set forth in claim 1. As detailed elsewhere

in this amendment, applicants do not believe this routine experimentation is undue experimentation.

With respect to paragraph 15 of the Office Action, the Examiner has stated "Screening for such compounds is an act of invention, for which insufficient guidance is provided in this Specification." As previously stated, applicants respectfully submit that the mere screening of compounds is a commonplace task requiring only routine skill in the art. Such an act is clearly not an act of invention. See, for example, *Consolidated Aluminum Corp. v. Foseco Int'l Ltd.*, 10 USPQ2d 1143, 1172 (N.D. Ill. 1988) and *Sewall v. Walters*, 21 F3d 411, 30 USPQ 2d 1356, 1359, (Fed. Circ. 1994). Moreover, the applicants respectfully submit they are not required to spell out how one of ordinary skill in the art would go about utilizing routine skill in the art to conduct such screenings.

> "...the law does not require a specification to be a Blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph." *Staehelin v Secher* 24 USPQ 2d 1513, 1516 (B.P.A.I. 1992) citing *In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA 1962).

With respect to paragraphs 16-19, applicants note that such paragraphs were included only "to illustrate the state of the art of Alzheimer's disease." However, included in these paragraphs are statements that could be taken to be claim rejections. In a good faith effort to be fully responsive, applicants hereby address these issues.

With respect to the general statement in paragraph 16, the instant invention is opposite to the "status quo" opinion, that is one aspect of what is novel about it. Delving deeper into the literature reveals a consistent lack of evidence that M1 agonists will be effective in treating AD, and that the opposite will work.

For example, United States Patent 6,391,871 states "it holds that hyperactivity of M3 muscarinic receptors plays an important role in neurofibrillary tangle formation and neuronal degeneration in Alzheimer's disease. This is in direct contradiction to a widely held presumption in the Alzheimer research field, which holds that the cholinergic muscarinic transmitter system is not hyperactive, but rather is hypoactive in Alzheimer's disease. The current application agrees with language in US Patent 6,391,871 that postsynaptic muscarinic antagonism will be beneficial, however, the current application is distinct from US Patent 6,391,871 in that it does not preferentially specify M3 receptor antagonism. Also the current application importantly specifies the co-administration of anticholinesterase to prevent an overall state of hypoactivity in the cholinergic system, whereas the process in US Patent 6,391,871 teaches against the adminstration of anticholinesterase (i.e., cholinesterease inhibitors), and furthermore states, "None of the safener agents proposed herein as effective treatments for Alzheimer's disease are classified as cholinesterase inhibitors, or are thought to possess any significant cholinesterase inhibitor activity."

Other recent work is partially at variance with the "cholinergic deficit hypothesis" of Alzheimer's disease and dementia. In the Religious Order Study, cholinergic enzymes in frontal cortex and hippocampus were increased in those having mild cognitive impairment, unchanged in those with mild AD and decreased with severe AD, as compared to normal controls (DeKosky ST, Ikonomovic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, Cochran EJ, Kordower JH, Mufson EJ.

Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann Neurol. 2002 Feb;51(2):145-55). These results, while suggesting a compensatory elevation in cholinergic systems in early dementia, nonetheless, support an eventual cholinergic deficit. With respect to paragraph 17, the applicants believe this rejection comes to the wrong conclusion because it is based on a selective review of the literature. While it is true that Fisher (2000) "Therapeutic Strategies in Alzheimer's Disease: M1 Muscarinic Agonists." Jpn. J. Pharmacol. 84:101-112 teaches muscarinic agonists may, in theory, be useful for treating Alzheimer's disease, these speculations are based on responses of cells in culture and animal models that do not fully replicate the disease. Clinical trials do not support the speculation of Fisher and others making similar predictions. In contrast to the prediction of Fisher and others, muscarinic agonists have been repeatedly shown to be ineffective in treating the cognitive decline associated with Alzheimer's disease. This inconsistency is even described by Fisher and colleagues. Fisher et al. "AF150(S) and AF267B: M1 Muscarinic Agonists as Innovative Therapies for Alzheimer's Disease", 2002, J. Mol. Neurosci. p. 145 state that: "some [M1] agonists show disappointing clinical results in AD".

Several M1 agonists have proved ineffective. The partial M1 muscarinic agonist and M2 muscarinic antagonist, Lu 25-109, was shown to be ineffective in treating Alzheimer's disease (Thal et al. 2000 "Lu 25-109, a muscarinic agonist, fails to improve cognition in Alzheimer's disease." Neurology 54:421). Lu 25-109 should be an ideal drug, because it stimulates postsynaptic M1 receptors and antagonizes presynaptic autoinhibitory M2 receptors. Hence both effects of Lu 25-109 act to increase acetylcholine activity. Similarly, the muscarinic agonist talsaclidine has been reported to be ineffective in ameliorating cognitive decline in Alzheimer's disease patients despite its producing decreased levels of amyloid β-peptide (Hook et al. 2003 "Treatment with the Selective Muscarinic Agonist Talsaclidine Decreases Cerebrospinal Fluid Levels of Total Amyloid β-Peptide in Patients with Alzheimer's Disease." Amyloid 10:1-6.; Wienrich M. et al. Pharmacodynamic profile of the M1 agonist talsaclidine in animals and man. Life Sci. 2001 Apr 27;68(22-23):2593-600). While it might be surprising that decreases in amyloid β-peptide are not accompanied by positive effects on cognition, it has been noted that the effectiveness of anti-amyloid treatments depends on the validity of the amyloid cascade hypothesis which is currently "unproven" (see Tariot PN, Federoff HJ. Current treatment for Alzheimer disease and future prospects. Alzheimer Dis Assoc Disord. 2003 Jul-Sep;17 Suppl 4:S105-13).

A multi-center trial of milameline was not completed due to the lack of efficacy shown by this muscarinic agonist (Jack et al. 2003, "MRI as a Biomarker of Disease Progression in a Therapeutic Trial of Milameline for AD" Neurology 60:253-260). Xanomeline, a M1 selective cholinergic agonist, was also shown to fail as a treatment for cognitive symptoms in Alzheimer's disease (Frederick et al., 2002 "Brain Proton Magnetic Resonance Spectroscopy in Alzheimer's Disease: Changes after Treatment with Xanomeline" Am. J. Geriatr. Psychiatry 10:81-88). Repeatedly, muscarinic agonists have failed to realize effectiveness in clinical trials that would be expected based on positive results in preclinical studies on laboratory animals. Applicants are not aware of a single instance where a cholinergic M1 agonist has been significantly effective in treating the cognitive symptoms of AD. The Alzheimer's Research Forum

[http://www.alzforum.org] lists all clinical trials on muscarinic agonists as discontinued (searched February 13, 2004). This includes AF102B, LU25-109, milameline and SB 202026.

The applicants' suggestion of using an antagonist, such as one for M1 receptors, is not entirely contraindicated by the speculations of Fisher and others. Applicants' invention teaches that cholinergic intervention must be regionally selective. The invention is to antagonize postsynaptic receptors (i.e., M1 muscarinic receptors) in order to decrease acetylcholine postsynaptic activity preferentially in limbic cortex where cholinergic activity stands to exacerbate dysfunctional activity; cholinergic activity in neocortex is to be maintained or increased. It is known that certain muscarinic antagonists exist which can preferentially inhibit cholinergic activity in limbic cortex (which includes hippocampus) while leaving cholinergic function in neocortex intact. The M1 selective antagonist dicyclomine was shown to inhibit hippocampus-dependent emotional memory, while leaving neocortex-dependent tone memory unaffected (Fornari RV, Moreira KM, Oliveira MG. Effects of the selective M1 muscarinic receptor antagonist dicyclomine on emotional memory. Learn Mem., 2000, 7:287-92). This study was done using normal rats having intact hippocampi and normal activity therein. In AD, the hippocampus is severely degenerated causing dysfunctional activity that can interfere with normal activity in other parts of the brain, such as the neocortex. Thus, inhibiting aberrant hippocampus-dependent activity and function stands to restore normal neocortical activity and normal neocortex-dependent memory function.

The principle of the applicants' invention is supported by data in the literature showing that lesions can sometimes enhance leaning and behavior, and that more extensive neuronal destruction can lead to more, not less, functional recovery (Irle E. An analysis of the correlation of lesion size, localization and behavioral effects in 283 published studies of cortical and subcortical lesions in old-world monkeys. Brain Res Brain Res Rev. 1990 Sep-Dec;15(3):181-213. Irle E. Lesion size and recovery of function: some new perspectives. Brain Res. 1987 Jul;434(3):307-20.) Partial damage to the limbic system impairs learning, whereas complete removal of limbic structures, including limbic cholinergic structures, has resulted in no measureable impairment to learning (Irle E. Combined lesions of septum, amygdala, hippocampus, anterior thalamus, mamillary bodies and cingulate and subicular cortex fail to impair the acquisition of complex learning tasks. Exp Brain Res. 1985;58(2):346-61; Irle E, Markowitsch HJ. Functional recovery after limbic lesions in monkeys. Brain Res Bull. 1990 Jul;25(1):79-92;). Applicants' invention is to simulate a quiescent limbic lobe through selective antagonism, and an M1 antagonist has the necessary characteristics to achieve this end. Another compound having necessary characteristics is an M1 antagonist with M3 agonist properties. The ratio of cortical/hippocampal receptors is greater for M3 receptors than it is for M1 receptors (Wei J, Walton EA, Milici A, Buccafusco JJ. M1-M5 muscarinic receptor distribution in rat CNS by RT-PCR and HPLC. J Neurochem. 1994 Sep;63(3):815-21; Tohyama M and Takatsuji K (eds) (1998) Atlas of Neuroactive Substances and Their Receptors in the Rat. Oxford University Press, New York.) Combining antagonist drugs, such as these, with an anticholinesterase will achieve the desired effect of enhanced cognition in the presence of hippocampal and limbic system degeneration. Applicants' invention teaches that a drug combination, such as a M1 receptor antagonist with an anticholinesterase, will inhibit limbic areas preferentially,

while preferentially activating other receptors (e.g., M3) in cortical areas, and that in this manner, this combination will facilitate other parts of the brain, such as the neocortex, in functioning more effectively.

Lastly, there is clinical evidence that atypical antipsychotic drugs, which antagonize acetylcholine, serotonin, norepinephrine and dopamine receptors, do improve cognition (i.e., memory). In particular, it was shown that atypical antipsychotic drugs with M1 antagonistic properties improve some types of memory in schizophrenic populations (Meltzer and McGurk, 1999, "The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia" Schizophr Bull. 25:233-55).

With respect to paragraph 18, is respectfully submitted that the phosphorylation of tau cannot be considered outside the context of its relationship with MAP-2. Fisher et al. (17 January 1996) "M1 Agonists for the treatment of Alzheimer's disease. Novel properties and clinical update." Ann. N.Y. Acad. Sci. 777:189-196 only focused upon the relationship between M1 agonists and tau. These studies were done on healthy CHO and PC12 cells in culture, not on degenerating AD brain cells. The applicants' invention stipulates that one consider the antagonist's effect on MAP-2 phosphorylation as primary in degenerating cells of AD brain. The central involvement of MAP-2 in Alzheimer's disease is demonstrated in Loring et al. (2001) "A Gene Expression Profile of Alzheimer's Disease" DNA Cell Biol. 2001 20:683-95; Erratum 2002, 21:243. Loring et al. (2001/2002) found a reduction in MAP-2 mRNA, but no change in tau mRNA or β-amyloid mRNA in post-mortem AD brain. These findings suggest MAP2 is affected before tau is affected in the disorder. Thus, the applicants' invention to indirectly antagonize MAP2 phosphorylation (e.g., by M1 antagonism) as the primary molecular site of treatment in AD brain is validated by the findings of Loring et al. (2001/2002).

Many studies indicate a complimentary relationship between MAP-2 and tau. Individual cells from AD brains that have accumulated altered tau in the form of PHF show a marked loss of MAP2 (Ashford et al., 1998. "Neuropil threads are collinear with MAP2 immunostaining in neuronal dendrites of Alzheimer brain" J Neuropathol Exp Neurol. 57:972-8). Transgenic mice overexpressing human tau do not accumulate insoluble hyperphosphorylated tau in neurons [which possess MAP-2], but do accumulate in glial cells [which lack MAP-2] (Higuchi et al., 2002 "Transgenic mouse model of tauopathies with glial pathology and nervous system degeneration" Neuron 35:433). Lastly, microtubules show changes in AD brain that cannot be attributed to tau (Cash et al., 2003, "Microtubule reduction in Alzheimer's disease and aging is independent of tau filament formation" Am J Pathol. 162:1623-7). This result argues for MAP2, which controls assembly of microtubules, as primary in the degenerative process in Alzheimer's disease, and tau and amyloid β-protein as secondary.

With respect to paragraph 19, applicants respectfully disagree with the Examiner. The applicants' invention specifies that antagonists, particularly M1 antagonists, which by the very nature of their preferential distribution in the limbic regions (e.g., frontal cortex, hippocampus), will be effective when administered along with an anticholinesterase. M1 receptor antagonism will inhibit dysfunctional activity in the limbic system and restore neocortical activity and function. An anticholinesterase will stimulate other muscarinic receptors (e.g., M3 muscarinic receptors) such that a complete hypocholinergic state is not induced. One of ordinary skill in the art would be able to

practice this claimed process by reading the specification without first partaking in undue experimentation.

20-25. THE EXAMINER HAS REJECTED CLAIMS 1-9 AS ALLEGEDLY FAILING TO MEET THE WRITTEN DESCRIPTION REQUIREMENT

The Examiner has rejected claims 1-9 stating:

> 20. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
>
> 21. The claims are drawn to a method of administering a neurotransmitter receptor antagonist which indirectly inhibits phosphorylation of microtubule-associated proteins-2 (MAP-2), causes the phosphorylation of MAP-2 in limbic cells, and causes the phosphorylation of MAP-2 in neocortical cells. The claims require specific biological activities which are contradictory. It is not clear how an antagonist can indirectly inhibit phosphorylation of MAP-2 while simultaneously leading to the phosphorylation of the same protein [in] two different cell populations. Thus, the claims are drawn to an ill-defined genus of antagonists which are defined by simultaneous and contradictory biological activities.
>
> 22. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is the aforementioned contradictory activities. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.
>
> 23. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is,

> for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see *Vas-Cath* at page 1116) As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.
>
> 24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian GFG's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.
>
> 25. Therefore the full breadth of the claims do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

With respect to paragraph 21, the Examiner has stated "The claims require specific biological activities which are contradictory. It is not clear how an antagonist can indirectly inhibit phosphorylation of MAP-2 while simultaneously leading to the phosphorylation of the same protein two different cell populations." The applicants respectfully respond that there is no contradiction. The appearance of contradiction may lie in the language, specifically that the antecedents differ in each case. In the first case, the clause "which inhibits phosphorylation..." refers to the antagonist. In the second and third cases "which leads to the phosphorylation" refers to the neurotransmitter receptors, which the antagonist inhibits. Although applicants are confident that the original wording is grammatically correct, applicants have rephrased the claim language from "antagonist of neurotransmitter receptor" to "neurotransmitter receptor antagonist" and from "which"to "that" in the second and third case. All changes are merely grammatical refinements and represent a good faith effort to comply with the Examiner's rejection. According to Strunk and White (2000) *The Elements of Style*. pg. 59, "The use of which for that is common in written and spoken language." The applicants respectfully submit that this rephrasing of claim language does not depart from the original intent, and does not constitute new matter.

If this was not the concern of the Examiner, Applicants respectfully submit that these two properties are not contradictory, but rather are accounted for by different levels of antagonist binding in different brain regions. Reference may be had, for example, to

the candidate drug disclosed on page 7, paragraph 2 of the specification as filed. Moreover, as is apparent to one of ordinary skill in the art, the various muscarinic receptors (M1 to M5) are found in differing concentrations in specific tissues within the body and in different brain regions. Applicants submit it is well within ordinary skill in the art to screen for a compound that preferentially favors a specific muscarinic receptor subtype in a selected bodily tissue. Examples of such preferences may be found, for example, in Ghelardini C.; Bartolini A.; Galeotti N.; Teodori E.; Gualtieri F.; S-(-)-ET 126: a potent and selective M1 antagonist in vitro and in vivo. *Life Science.* **1996**;58(12):991-1000. Since applicants have submitted examples of compounds which contain both of these properties, such properties clearly cannot be contradictory. Applicants respectfully submit that the Examiner's rejection has been obviated.

With respect to paragraph 22, the Examiner has stated "The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation." Applicants note that "The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" citing *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111. The claims are drawn to a process. It is unclear how a process claim could contain a "structure that must be conserved."

With respect to paragraph 23, the Examiner has stated "As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required." Applicants note their claims are drawn to a process, and not a compound. The Examiner has noted in paragraph 23 that "The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" citing *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111. Applicants respectfully submit they must show possession of the process of the invention, and not possession of a compound, as a compound is not being claimed. It is the belief of the applicants that possession of the invention has already been shown in the specification. See, for example, Figure 2 of the application as filed and the corresponding description in the specification found beginning on page 19.

M.P.E.P § 2163 (III)(A) outlines the actions to be taken if an Examiner believes a claim fails to be supported by the specification for lack of a written description by stating:

> In rejecting a claim, the examiner must set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:
> (A) Identify the claim limitation at issue; and
> (B) Establish a prima facie case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of 'unpredictability in the art' is not a sufficient reason to support a rejection for lack of adequate written description.

Applicants note the only claim limitations the examiner identified were the supposed contradictory elements of "indirectly inhibit phosphorylation of MAP-2 while simultaneously leading to the phosphorylation of the same protein two different cell populations." Applicants have already demonstrated that such properties are, in fact, not contradictory, as evidenced by the cited examples. It is the belief of the applicants that this clarification is fully responsive to the Examiner's Written Description rejection.

26-28. THE EXAMINER HAS REJECTED CLAIMS 1 AND 4 AS ALLEGEDLY INDEFINITE

The Examiner has rejected claims 1 and 4 stating:

> 26. Claims 1 and 4 are rejected under 25 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
> 27. The term "indirectly inhibits" in claim 1 is a relative phrase which renders the claim indefinite. The term "indirectly inhibits" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of what is meant by "indirectly inhibits" is not clear from the Specification or the prior art.
> 28. The term "most current" in claim 4 is a relative term which renders the claim indefinite. The term "most current" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of what is mean by "most current" is not clear from the Specification or the prior art.

The Examiner has rejected claim 1 on the grounds that the term "indirectly inhibits" renders the claim indefinite. It is submitted that indirect inhibition is a term of art which one of ordinary skill would clearly understand. Indirect merely describes a set of steps whereby a said antagonist first binds a membrane receptor, then prevents activation of a linked G-protein, then prevents activation of a second messenger cascade, and then prevents activation of a protein kinase, rendering the protein kinase unable to phosphorylate MAP-2. These steps are well known to those of ordinary skill. As such, using the term indirect does not render the claim indefinite. However, to facilitate prosecution of this application, applicants have amended claim 1 to delete the term "indirect" as it is not necessary to point out these steps to anyone of ordinary skill. It is respectfully submitted that the Examiner's rejection has been obviated.

The Examiner has rejected claim 4 on the grounds that the term "most current" renders the claim indefinite. Applicants have rephrased the claim language in a good faith effort to comply with the Examiner's rejection. The applicants respectfully submit that this rephrasing of claim language does not depart from the original intent, and does

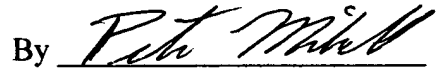
not constitute new matter. It is respectfully submitted that the Examiner's rejection has been obviated.

CONCLUSION

If applicants are denied patent protection for an invention that is admittedly novel and unobvious, as evidenced by the lack of prior art rejections, the applicants would respectfully pose the question "Is this fair?" Would a competitor wish to take this specification and practice the claimed process? It is respectfully submitted that there is sufficient disclosure in the specification as filed to enable such a competitor to practice the invention without the assistance of the inventors. If the inventors are denied the protection of a patent, then they would have revealed their novel and unobvious process for nothing.

Applicants respectfully request reconsideration and that a timely Notice of Allowance be issued in this case. If, for any reason, the Patent Examiner believes that a telephone conference with applicant's agent might in any way facilitate the prosecution of this case, the Examiner is respectfully requested to call such agent.

Respectfully submitted,
Howard J. Greenwald P.C.

By 

Peter J. Mikesell
Reg. No. 54,311
Telephone (585) 387-0285
Fax (585) 387-0288